Stability of Ethylcellulose Barrier Membrane Coated Hydrochlorothiazide Matrices Comprising Starch1500® or Lactose as Filler

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Poster Reprint
AAPS 2012

Purpose

Hydrophilic matrices (HM) are a very popular and widely used formulation option for oral extended release (ER) drug delivery. To ensure complete release of insoluble drugs from HM, formulation with low viscosity grades of hypromellose are generally recommended.[1,2] One of the challenges associated with HM is the potential *food effect* observed with low solubility drugs; drug release may be different when taken with food versus on an empty stomach.[3] The application of insoluble barrier membrane (BM) coating over matrix tablets was found to be a successful approach in eliminating the observed drug release variability and potential food effect as presented in the earlier studies.[4,5] In this study, the effect of stability conditions on drug release from an ethylcellulose BM coated HM of hydrochlorothiazide (HCTZ), using lactose as a soluble filler or partially pregelatinized starch (Starch 1500®) as a partially soluble filler, was investigated.

Experimental Methods

Formulation and Tablet Preparation

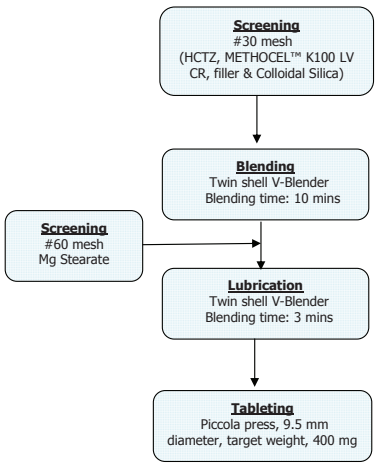
The composition of HCTZ hydrophilic matrix tablets is shown in Table 1. METHOCEL™ K100LV CR was used as the rate controlling polymer, with fillers of varying solubility, lactose or Starch 1500.

Table 1. Composition of Extended Release HCTZ Matrix Tablets

Ingredients	Supplier	Composition (%w/w)	
		Starch 1500	Lactose
Hydrochlorothiazide (HCTZ)	Hubei Maxpharm, China	50.0	50.0
Hypromellose (METHOCEL™ K100 LV Premium CR)	The Dow Chemical Company, USA	30.0	30.0
Partially pregelatinized starch (Starch 1500)	Colorcon, USA	19	-
Lactose monohydrate (FastFlo®)	Foremost, USA	-	19
Colloidal silicon dioxide (Cab-O-Sil® M5P)	Cabot Corp., USA	0.5	0.5
Magnesium stearate	Mallinckrodt, USA	0.5	0.5
	Total	100.0	100.0

HCTZ matrix tablets were prepared as shown in Figure 1.

Figure 1. Process Flow Chart for Production of HCTZ (200 mg) Matrix Tablets



Tablets of sufficient mechanical strength [hardness (tensile strength) > 15 kP (3.4 MPa)] were used for BM coating application.

Application of Barrier Membrane Coating

HCTZ matrix tablets were coated with an insoluble barrier membrane using aqueous ethylcellulose dispersion (Surelease®) with Opadry® coating (HPMC-based) as pore-former, weight ratio of 85:15. Prior to application, the coating systems were dispersed in water at 10% w/w solids content. Tablets were coated to 2% weight gain (WG) in a 12" fully-perforated coating pan (Labcoat I, O'Hara Technologies, Canada) using a 1 mm spray gun (970/7-1S 75, Schlick, Germany). The recommended coating process parameters for Surelease were used for application of the BM coating (Table 2).

Stability Study

BM coated HCTZ matrix tablets were packaged in HDPE bottles, with desiccant, heat sealed and placed on stability at 30°C/65% RH and 40°C/75% RH for 6 months. The samples were pulled at designated time intervals and tested for physical attributes and drug release profiles.

Dissolution Studies

In vitro dissolution studies were conducted using Apparatus II (100 rpm) with sinkers in 900 mL of media; pH 4.5 acetate buffer for 4 hr, followed by pH 6.8 phosphate buffer for 12 hr. HCTZ release was determined spectrophotometrically at a wavelength of 272 nm. Drug release profiles were compared using similarity factors (f_2).

Table 2. Coating Process Parameters

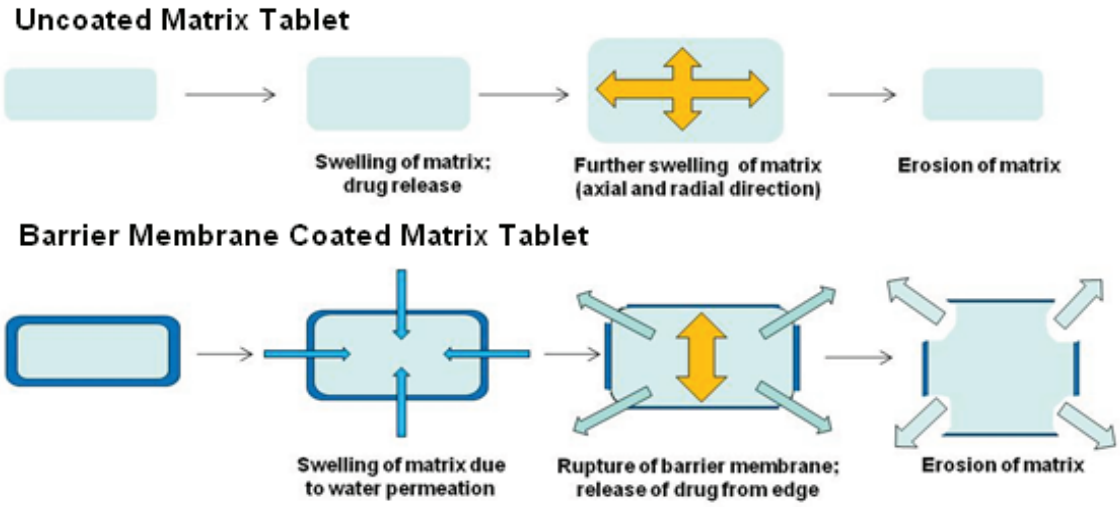
Parameter	Value
Tablet charge (kg)	1
Inlet temperature (°C)	55-57
Bed temperature (°C)	42-45
Exhaust temperature (°C)	47-49
Air flow (m^3/hr)	290
Spray rate (g/min)	6-8

Results

The dispersion viscosity and pH of the Opadry 300 coating composition was determined at solids levels up to 25%, as shown in **Figure 1**. The dispersion viscosity is well below the commonly accepted viscosity threshold of about 400 cP, indicating that this coating system is capable of application at solids in excess of 25%.

The performance and fate of uncoated and BM coated matrices on exposure to dissolution media, is shown in Figure 2.

Figure 2. Performance of Uncoated and BM Coated Matrices in Dissolution Media



The drug release profiles of uncoated HCTZ matrix tablets showed first order drug release, while application of BM coating resulted in near zero order HCTZ release. Figures 3 and 4 exhibit the drug release from BM coated matrix tablets containing soluble filler (lactose) at initial time point, as well as upon storage at 30°C/65% RH and 40°C/75% RH conditions, respectively.

BM coated matrix formulations containing lactose or Starch 1500 resulted in similar drug release under exposure to the stability conditions (Table 3). However, the matrices formulated with soluble filler lactose resulted in higher variability of drug release as evident from the greater standard error bars (average value: 3.9%, range: 0-10.2%). The highest extent of variability was noted at 8-14 hours of drug release from these matrix tablets (average value: 6.4%, range: 3.1-10.2%).

Inclusion of Starch 1500, partially soluble filler, in HCTZ matrix tablets led to reduction of variability in drug release as evident from the smaller error bars as shown in Figure 5 and 6 (average value: 3.1%, range: 0-7.8%). Furthermore, the reduction in variability of drug release was also observed particularly between 8-14 hrs (average value: 4.5%, range: 2.5-7.8%). Such robust drug release may be attributed to a potential synergistic effect of Starch 1500 and METHOCEL as reported in the literature.[6] The drug release profiles of both the Starch 1500 and lactose containing matrices remained similar compared to the respective time zero dissolution profiles after storage for 6 months (f_2 > 50 in both cases; Table 3).

Table 3. Comparison of Similarity Factors (f_2) for BM coated HCTZ Tablets (release profiles for each filler, at the initial time point was considered as reference)

Stability Condition	Duration	Starch 1500	Lactose
40°C/75% RH	3 months	85	77
	6 months	65	64
30°C/65% RH	3 months	94	60
	6 months	63	52

Figure 3. Dissolution Profiles of HCTZ (200 mg) ER Matrix Tablets Containing Lactose as a Filler and BM Coating at 2% WG after storage at 30°C/65% RH

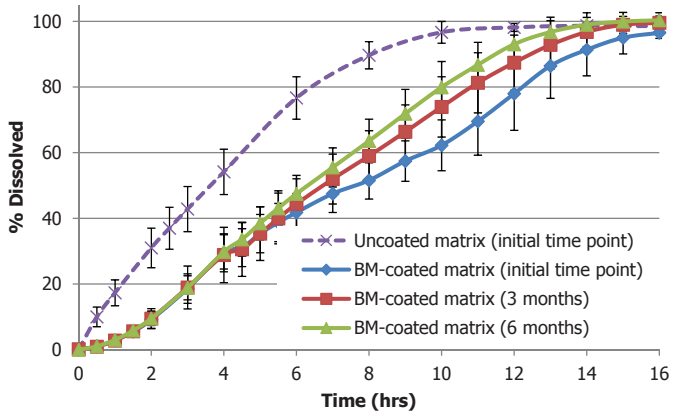


Figure 4. Dissolution Profiles of HCTZ (200 mg) ER Matrix Tablets Containing Lactose as a Filler and BM Coating at 2% WG after storage at 40°C/75% RH

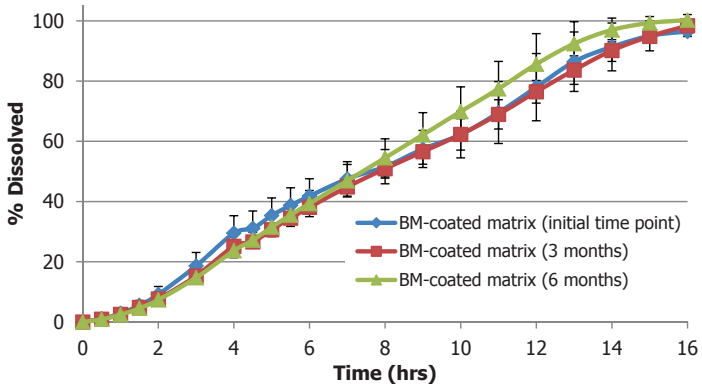


Figure 5. Dissolution Profiles of HCTZ (200 mg) ER Matrix Tablets Containing Starch 1500 as a Filler and BM Coating at 2% WG after storage at 30°C/65% RH

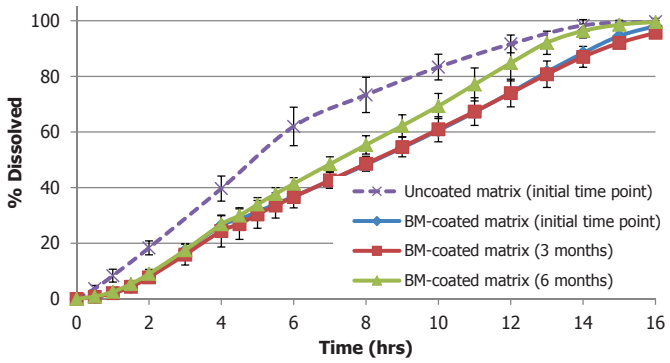
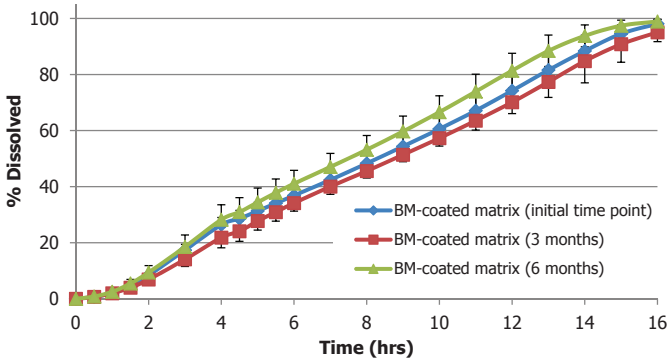


Figure 6. Dissolution Profiles of HCTZ (200 mg) ER Matrix Tablets Containing Starch 1500 as a Filler and BM Coating at 2% WG after storage at 40°C/75% RH



Conclusions

BM coated hydrophilic matrices are a promising formulation option for obtaining controlled and robust drug release, which may also mitigate the food effect. BM coated HCTZ matrices, with either Starch 1500 or lactose as a filler, provided consistent and stable drug release profiles irrespective of the storage conditions. Use of Starch 1500 as a filler within the formulation also contributed to additional robustness of the matrix tablets.

References

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